# WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
Uppsala, Sweden

*The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as partners in WHO. The information is produced in the form of résumés in English, full texts of which may be obtained on request.*

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**No 2, 2009**

In this issue, we report the suspension of efalizumab in Europe and elsewhere, and the withdrawal of fenfluramine in China. We bring you information on risks and restrictions with some group products (anticonvulsants, antipsychotics, bisphosphonates, SSRIs etc) and advice on some individual drugs in the section on Safety of Medicines. The Feature section includes a short report from the nineteenth meeting of the Global Advisory Committee on Vaccine Safety.

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## Safety of medicines



## Feature

## Aliskiren

### New contraindication and warning

**Europe.** The European Medicines Agency (EMEA) has recommended adding a contraindication to the Product Information for aliskiren, which states that it is not to be used in patients who have experienced angioedema when taking aliskiren in the past. The Agency has also recommended including a warning, stating that patients who develop signs of angioedema should stop treatment and seek medical attention. Aliskiren is authorized for the treatment of essential hypertension.

According to the EMEA, there were reports of cases of angioedema or similar reactions in association with aliskiren-containing medicines. The EMEA's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of aliskiren-containing medicines in the treatment of essential hypertension outweigh their risks, but that angioedema can occur as a rare and serious adverse effect.

***Reports in WHO Global Individual Case Safety Reports (ICSR) database, VigiBase: Aliskiren***

*A total of 54 reports of angioedema*

***Reference:***
*Press Release, EMEA, 19 February 2009 (www.emea.europa.eu).*

## Atomoxetine

### Risk of psychotic or manic symptoms

**UK**. The Medicines and Healthcare products Regulatory Agency (MHRA) has alerted that atomoxetine can be associated with treatment-emergent psychotic or manic symptoms, including hallucinations, delusional thinking, mania and agitation, in children and adolescents without a history of psychotic illness or mania. Health-care professionals have been advised to consider a possible causal role of atomoxetine and discontinuation of treatment, if such symptoms occur. Atomoxetine (Strattera) is a selective noradrenaline reuptake inhibitor, authorized for use in the treatment of attention-deficit/hyperactivity disorder (ADHD) as part of a comprehensive treatment regimen.

Product information for prescribers has been updated to reflect the safety information.

***Reference:***
*Drug Safety Update, MHRA, Volume 2, Issue 8, March 2009 (www.mhra.gov.uk).*

## Cough and cold medicines

### New advice on use of over-the-counter cough and cold medicines for children

**Kenya (1).** The Kenya Pharmacy and Poisons Board (PPB) stated that the following over-the-counter (OTC) cough and cold medicines are not recommended in children under six years of age:
• Antitussives (dextromethorphan and pholcodine)
• Expectorants (guaifenesin and ipecacuanha)
• Nasal decongestants (ephedrine, oxymetazoline, phenylephrine, pseudoephedrine and xylometazoline)
• Antihistamines (brompheniramine, chlorpheniramine, diphenhydramine, doxylamine, promethazine and tripolidine).

Cough and cold medicines containing these ingredients will be available for children between ages 6 to 12 years, but only in pharmacies.

The PPB notes that these medicines provide only symptomatic treatment and that there is no information that they are really effective. Serious and potentially life-threatening side effects can occur, if these medicines are taken inappropriately: these include death, convulsions, increased heart rates and reduced levels of consciousness.

**UK (2).** The Medicines and Healthcare products Regulatory Agency (MHRA) has announced a comprehensive package of measures to promote the safer use of OTC cough and cold medicines for children under 12 years, based on the advice from the Commission on Human Medicines.

The MHRA has recommended that parents and carers should no longer use OTC cough and cold medicines in children under the age of six, because there is no evidence that these medicines work and due to the fact that they can cause side effects such as allergic reactions, effects on sleep or hallucinations. For six to 12 year old children, the Agency says that these medicines will continue to be available but only in pharmacies, with clearer advice on the packaging and from the pharmacist. This is because the risks of side effects is reduced in older children since they weigh more, get fewer colds and can say if the medicine is doing any good. More research is being done by industry on how well these medicines work in children aged six to 12 years.

Some combinations which are illogical (such as cough suppressants and expectorants) are being phased out, and all liquid cough and cold medicines

will be packaged in child resistant containers.

The products affected are the medicines containing the following active ingredients:
- Antitussives: dextromethorphan and pholcodine
- Expectorants: guaifenesin and ipecacuanha
- Nasal decongestants: ephedrine, oxymetazoline, phenylephrine, pseudoephedrine and xylometazoline
- Antihistamines: brompheniramine, chlorphenamine, diphenhydramine, doxylamine, promethazine and tripolidine.

The labelling will be updated and the legal status of medicines authorized for children aged six to 12 years will be changed from general sale to pharmacy.

*(See WHO Pharmaceuticals Newsletter No. 4, 2007 for a public health advisory regarding OTC cough and cold medicines for use in children in the USA).*

***References:***

*(1) Statement on cough and cold medicines, Frequently Asked Questions, PPB, 13 March 2009 (www.pharmacyboardkenya.org)*
*(2) Safety information, MHRA, 28 February 2009 (www.mhra.gov.uk).*

## Efalizumab

### Suspension of marketing authorization recommended in Europe and other countries

**Canada (1).** Health Canada has issued recommendation to suspend efalizumab (Raptiva) in Canada, after the EMEA has determined that the benefit/risk for the product has become unfavourable due to safety concerns.

Prescribers in Canada are advised not to issue any new prescriptions for efalizumab (Raptiva) and to review the treatment of patients taking this medicine to assess the most appropriate alternative. The public are warned not to change or stop their treatment without first consulting doctors because abrupt discontinuation of the medicine without alternative treatment may be followed by a return of psoriasis or onset of new psoriasis.

*(See WHO Pharmaceuticals Newsletter No. 1, 2009 for warnings of progressive multifocal leukoencephalopathy (PML) in Canada and UK).*

**Europe (2).** The EMEA has recommended the suspension of the marketing authorization for efalizumab (Raptiva), which is authorized to treat adult patients with moderate to severe chronic plaque psoriasis, following the opinion of the CHMP that the risks of this medicine outweigh its benefits. The CHMP reviewed the reports of serious side effects, including three confirmed cases of PML in patients who had taken efalizumab (Raptiva) for more than three years. Two out of the three cases resulted in death. There was also a suspected case of PML reported.

The CHMP concluded the following:
- Efalizumab (Raptiva)'s benefits are modest.
- In addition to PML, efalizumab (Raptiva) is associated with other serious side effects, including Guillain-Barré and Miller-Fisher syndromes, encephalitis, encephalopathy, meningitis, sepsis and opportunistic infections.
- There is not enough evidence to identify a group of patients in which the benefits of efalizumab (Raptiva) outweigh its risks, in particular there is a lack of data on effectiveness and safety in patients who have no other treatment options and who may already have a weakened immune system as a result of previous treatments.

The EMEA has advised prescribers not to issue any new prescriptions for efalizumab (Raptiva) and to review the treatment of patients currently receiving the medicine to assess the most appropriate alternative.

*(Also see WHO Information Exchange System Alert No. 121, Drug Alert URL: www.who.int/medicines)*

**Switzerland (3).** The Swiss Agency for Therapeutic Products (Swissmedic) has announced its intention to suspend authorization of efalizumab (Raptiva), following EMEA's recommendation of the suspension of the marketing authorization for the product.

Swissmedic has recommended that physicians should no longer issue any new prescriptions for efalizumab (Raptiva). The Agency has also warned that control by a physician is necessary to change the treatment for patients currently using the product, adding that stopping the product abruptly on a patient's own initiative can lead to an acute worsening of psoriasis and symptoms of inflammation.

**USA (4).** The United States Food and Drug Administration (US FDA) has issued a Public Health Advisory to notify health-care professionals of three confirmed cases and one possible case of PML in patients treated with efalizumab (Raptiva), and to provide recommendations for health-care providers and patients when treatment with this product is considered.

The US FDA says that it will take appropriate steps to minimize the risks from efalizumab, and ensure that patients prescribed the product are clearly informed of the signs and symptoms of PML, and that health-care professionals carefully monitor patients for the possible development of PML.

In October 2008, the product labelling was revised to highlight the risks of life-threatening infections including PML in a Boxed Warning. The US FDA also directed the manufacturer to develop a Risk Evaluation and Mitigation Strategy (REMS) to include a Medication Guide to ensure that patients receive risk information about the medicine.

(Argentina and Turkey have informed WHO that the authorization/commercialization of efalizumab (Raptiva) has been suspended in their countries).

***Reports in WHO Global ICSR database, VigiBase: Efalizumab***

*Central and peripheral nervous system disorders: 461*
*Encephalopathy (including encephalitis) 4*
*Meningitis 40*
*Polyneuropathy 5*
*Neuritis (Miller-Fisher syndrome) 11*

*Resistance mechanism disorders: 166*
*Sepsis 18*
*Infection (including bacterial, fungal, secondary, staphylococcal, susceptibility increased, and viral) 69*

***References:***

*(1). Advisories, Warnings and Recalls, Health Canada, 20 January 2009 (www.hc-sc.gc.ca).*
*(2). Press Release, EMEA, 19 February 2009 (www.emea.europa.eu).*
*(3). Announcements, Swissmedic, 20 February 2009 (www.swissmedic.ch).*
*(4). Media Release, US FDA, 19 February 2009 (www.fda.gov).*

## Exenatide

### Risk of severe pancreatitis and renal failure

**UK.** The MHRA has announced that suspected adverse reaction reports of necrotising and haemorrhagic pancreatitis, some of which were fatal, have been received in association with exenatide (Byetta). Health-care professionals have been advised that if pancreatitis is diagnosed, exenatide should be permanently discontinued. Exenatide is indicated for treatment of type 2 diabetes mellitus in combination with metformin.

According to the Agency, up to February 2009, six case reports of pancreatitis and a further three cases of acute pancreatitis were reported in the UK. There have been approximately 800 000 patient-years of exposure worldwide since licensing. Up to September 2008, 396 case reports of pancreatitis have been received worldwide and 80% of these reports were considered to be possibly related to exenatide, and in several cases there was evidence of positive rechallenge. Nine reports of necrotising or haemorrhagic pancreatitis have been received worldwide, two of which had a fatal outcome. After a Europe-wide review, product information for exenatide is being updated to include further information about this risk.

Up to 30 January 2009, there were seven case reports of acute renal failure in the UK in association with exenatide. The Agency has emphasized that exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment.

***Reference:***

*Drug Safety Update, MHRA, Volume 2, Issue 8, March 2009 (www.mhra.gov.uk).*

## Fenfluramine

### Withdrawal of the drug approval

**China**. According to the State Food and Drug Administration (SFDA), fenfluramine hydrochloride (including raw materials) will be withdrawn from China's market because of the risk of causing heart valve damage and pulmonary arterial hypertension. The production, sale and use of fenfluramine hydrochloride (including raw materials) will be suspended, and the drug approval number has been revoked.

***Reference:***

*Media Release, SFDA, 12 January 2009 (eng.sfda.gov.cn/eng/)*

## Fluoroquinolones

### Boxed warning about tendon disorders

**Kenya.** The PPB has alerted that fluoroquinolones are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. The Agency has informed prescribers and other stakeholders that the Committee on Drug Registration (Human) has recommended that all fluoroquinolones should include a boxed warning on the package, patient information leaflet and prescriber information leaflet with this information.

*(See WHO Pharmaceuticals Newsletters No. 3, 2008 and No. 1, 2003 for a boxed warning against increased risk of tendinitis and tendon rupture in the USA and reports of tendon disorders in Australia, respectively)*

***Reference:***
*Fluoroquinolones and tendon disorders: letter from PPB, 3 March 2009.*

## Metoclopramide

### Warning against chronic use

**USA**. The US FDA has required manufacturers of metoclopramide to add a boxed warning to the labels about the risk of its long-term or high-dose use. Chronic use of metoclopramide has been linked to tardive dyskinesia. Those at greatest risk include the elderly, especially older women, and people who have been taking the drug for a long time. Metoclopramide is used as a short-term treatment of gastroesophageal reflux disease and diabetic gastroparesis. It is recommended that treatment not exceed three months. The Agency has become aware of continued spontaneous reports of tardive dyskinesia in patients who used metoclopramide and the majority of them had taken the drug for more than three months.

Manufactures will be required to implement REMS for metoclopramide-containing drugs to ensure that patients are provided with a medication guide that discusses this risk.

***Reports in WHO Global ICSR database, VigiBase: Metoclopramide***

*A total of 362 reports of dyskinesia tardive*

***Reference:***
*FDA News, US FDA, 26 February 2009 (www.fda.gov).*

## Mycophenolate mofetil

### Introduction of Medication Guide

**USA**. The US FDA and Roche Laboratories Inc. notified health-care professionals of the introduction of a Medication Guide for mycophenolate mofetil (CellCept) to provide important safety information in a language that patients can easily comprehend. Pharmacists are required to distribute a copy of the Medication Guide to every patient who fills a prescription of this product. The US FDA has also required the introduction of a Medication Guide for mycophenolic acid (Myfortic) marketed by Novartis.

The Medication Guide states that the product can cause serious side effects including possible loss of pregnancy and higher risk of birth defects, and increased risk of getting serious infections and certain cancers.

*(See WHO Pharmaceuticals Newsletters No. 2, 2008 and No.6, 2007 for reports of PML in Europe and USA, and risk of pregnancy loss and congenital malformations in USA, respectively.)*

***Reference:***
*Media Release, US FDA, 12 February 2009* (www.fda.gov).

## Natalizumab

### Updated information on PML

**Canada.** Health-care professionals have been notified that the occurrence of post-marketing reports of PML in patients receiving natalizumab (Tysabri) monotherapy, including the typical symptoms of PML, has been included in the Canadian Product Monograph. The product is authorized as monotherapy for the treatment of patients with relapsing-remitting multiple sclerosis. PML is a known risk of this product. Combination therapy is contraindicated.

Since the product became available on the market worldwide, five confirmed cases of PML have been reported in patients receiving natalizumab (Tysabri) monotherapy. One case had a fatal outcome. As of the end of December 2008, approximately 37 600 patients were receiving the medicine worldwide.

*(See WHO Pharmaceuticals Newsletter No. 4, 2006 for elements of the risk management programme for natalizumab in USA.)*

***Reference:***
*Advisories, Warnings and Recalls, Health Canada, 13 January 2009 (www.hc-sc.gc.ca).*

## Phosphodiesterase type 5 inhibitors

### Risk of sudden hearing loss

**New Zealand**. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) advised prescribers of the risk of sudden hearing loss associated with phosphodiesterase type 5 (PDE-5) inhibitors (sildenafil, tadalafil, vardenafil). As of 30 April 2008, the Centre for Adverse Reactions Monitoring received three reports of sudden decrease or loss of hearing with sildenafil (2) and tadalafil (1). The data sheets for these medicines have been updated to provide prescribers with information on the risk and steps to take in the event of sudden hearing loss.

***Reference:***
*Prescriber Update Vol. 30, No.1, February 2009* (www.medsafe.govt.nz).

## Zonisamide

### Alert on metabolic acidosis

**USA.** Following a review of updated clinical data, the US FDA has alerted that treatment with zonisamide can cause metabolic acidosis in some patients. Zonisamide is indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy. Metabolic acidosis can result in hyperventilation, and non-specific symptoms such as fatigue and anorexia, or more severe symptoms including cardiac arrhythmias or stupor. Chronic metabolic acidosis can have adverse effects on kidneys and bones and retard growth in children. According to the Agency, patients with predisposing conditions or therapies may be at greater risk for developing metabolic acidosis following treatment with the medicine. The risk of zonisamide-induced metabolic acidosis appears to be more frequent and severe in younger patients.

Health-care professionals have been advised to measure serum bicarbonate before starting treatment and periodically during the treatment with the drug. The US FDA is working with the manufactures to revise the product labelling to reflect this safety information.

***Reference:***
*Information for Healthcare Professionals, US FDA, 19 February 2009* (www.fda.gov).

## Anticonvulsants

### Risk of congenital malformations

**New Zealand.** Medsafe has alerted prescribers of the risk of congenital malformations associated with the use of anticonvulsants (anti-epileptics) during pregnancy, and recommended that the most effective medicine should be used at its lowest effective dose.

In addition, Medsafe says that it is important that all women of child-bearing age taking anticonvulsants receive counselling on the risk of congenital malformations associated with the use of anticonvulsants.

***Reference:***
*Prescriber Update Vol. 30, No.1 February 2009 (www.medsafe.govt.nz).*

## Antipsychotics

### Increased mortality risk

**New Zealand (1).** Medsafe has warned that the risk of death is significantly increased in elderly patients with dementia who are prescribed conventional antipsychotics, compared with non-users. The risk appears to be similar to, or possibly greater than, the risk with atypical antipsychotics.

Medsafe advised prescribers that the use of antipsychotics in elderly dementia patients should only be considered after a careful assessment of the risks and benefits of treatment.

**UK (2).** MHRA has advised that there is a clear increased risk of stroke and a small increased risk of death when antipsychotics (typical or atypical) are used in elderly people with dementia. Only one antipsychotic, risperidone (Risperdal) is licensed for short-term treatment of persistent aggression in Alzheimer's dementia with certain conditions.

In addition, the Agency recommends that health-care professionals should carefully assess the risks and benefits associated with risperidone treatment for every patient, taking into consideration the known increased mortality rate associated with antipsychotic treatment in the elderly, and that they should consider the risk of cerebrovascular events before treating patients with risperidone.

***References:***
*(1). Prescriber Update Vol. 30, No.1, February 2009 (www.medsafe.govt.nz).*
*(2). Drug Safety Update, MHRA, Volume 2, Issue 8, March 2009 (www.mhra.gov.uk).*

## Black cohosh

### Reports of hepatotoxicity

**New Zealand.** Medsafe has issued information on reports of hepatotoxic reactions in association with the use of the herb black cohosh (*Cimicifuga racemosa*) that is used for the relief of menopausal symptoms. Reported reactions include abnormal or elevated liver function test results, hepatitis, and hepatic failure sometimes requiring liver transplantation.

The Authority advised prescribers to look for signs of liver toxicity in patients taking black cohosh.

*(See WHO Pharmaceuticals Newsletter No. 4, 2006 for reports of hepatotoxicity in Europe.)*

***Reference***:
*Prescriber Update Vol. 30, No.1, February 2009 (www.medsafe.govt.nz).*

## Bisphosphonates

### Risk of atypical stress fractures

**UK.** Following a Europe-wide review of bisphosphonates and atypical stress fractures, the MHRA has warned that atypical stress fractures of the proximal femoral shaft have been reported in patients treated long-term with alendronic acid. Bisphosphonates are used for prophylaxis and treatment of osteoporosis, treatment of Paget's disease, and as part of some cancer regimens. Health-care professionals have also been advised that patients who develop atypical stress fractures should discontinue alendronic acid and receive no further bisphosphonate treatment unless the benefits clearly outweigh the risks. The possibility that other bisphosphonates may be associated with an increased risk of atypical stress fractures cannot be excluded.

Product information for alendronic acid will be updated to include a warning about atypical stress fractures.

*(See WHO Pharmaceuticals Newsletters No. 1, 2008, No.5, 2006 and No.6, 2004 for alert on musculoskeletal pain in USA, reports of osteonecrosis of the jaw in Australia, and reports of osteonecrosis of the jaw in USA, respectively.)*

***Reference:***
*Drug Safety Update, MHRA, Volume 2, Issue 8, March 2009 (www.mhra.gov.uk)*

## Botulinum toxin type A

### Adverse reactions such as muscle weakness

**Australia.** The Australian Adverse Drug Reactions Advisory Committee (ADRAC) and the Therapeutic Goods

Administration (TGA) have emphasized the importance of adherence to the indications and dosing instructions for use of botulinum toxin-containing products. Botulinum toxin type A (Botox, 100 U/vial) is used for the treatment of strabismus, blepharospasm and facial nerve disorders, spasmodic torticollis, various spasticity disorders, spasmodic dysphonia, axillary hyperhidrosis, and treatment of brow furrow lines. A haemag-glutinin complexed form of botulinum toxin type A (Dysport, 500 U/vial) has similar but more limited indications.

Since mid 1994, the TGA has received 45 reports in connection with the use of botulinum toxin, none of which have described a fatal outcome. The reactions reported most commonly are of muscle weakness (16 cases) at sites adjacent to or distant from the injected area, including dysphagia (8 reports), respiratory failure or dyspnoea (3) and generalized muscle weakness (7). Other reactions include rash or other allergic reaction, diplopia and fatigue. Seven reports cited off-label use and 17 cited use for cosmetic reasons, but the others cited use according to approved indications.

ADRAC and the TGA say that most adverse effects with botulinum toxin appear to be non serious and transient, based on Australian and other countries' experience. Serious adverse reactions are rare and usually relate to spread of the toxin to non-target areas, generally attributed to excessive volume of injection.

*(See WHO Pharmaceuticals Newsletter No. 1, 2009 for warning about distant toxin spread in Canada.)*

***Reference:***
*Australian Adverse Drug Reactions Bulletin, Volume 28, Number 1, February 2009 (www.tga.gov.au).*

## Clopidogrel

### Effects of genetic factors and other drugs on the effectiveness of clopidogrel

**USA**. The US FDA has notified health-care professionals that the manufacturers of clopidogrel bisulfate (Plavix), which is an antiplatelet drug, have agreed to work with the Agency to conduct studies to obtain information about the effects of genetic factors and other drugs, especially proton pump inhibitors (PPIs) on the effectiveness of clopidogrel. There are published reports that clopidogrel is less effective in some patients than it is in others. Differences in effectiveness may be due to genetic differences in the way the body metabolizes the drug or due to the fact that certain other drugs taken concomitantly with clopidogrel can interfere with its metabolism.

Until further information is available, the US FDA recommends that health-care providers should continue to prescribe and patients should continue to take clopidogrel as directed, because the drug has demonstrated benefits in preventing blood clots. The Agency also advises health-care providers to re-evaluate the need for starting or continuing treatment with a PPI, including over-the-counter drugs, in patients taking clopidogrel.

***Reference:***
*Early Communication about an Ongoing Safety Review, US FDA, 26 January 2009* (*www.fda.gov*).

## Dietary supplement containing undeclared drug

### Warning about health risk

**USA**. The US FDA has warned consumers not to take a product named Venom HYPERDRIVE 3.0, which was sold as a dietary supplement and containing undeclared sibutramine. Sibutramine is a controlled substance with risks for abuse or addiction and poses potential safety risks such as increase in blood pressure and heart rate. The product was sold in the United States of America as well as in Australia, Canada, France, Hungary, Poland, South Africa, Sweden, the Netherlands and the United Kingdom, according to the Agency.

***Reference***:
*FDA News, US FDA, 27 January 2009 (www.fda.gov).*

## Drotrecogin alfa (activated)

### Increased risk of serious bleeding events and death

**USA**. The US FDA has informed the public of its ongoing safety reviews of drotrecogin alfa (activated) (Xigris), indicated for the reduction of mortality in adult patients with severe sepsis who have a high risk of death. The Agency refers to a retrospective study (*Gentry et al.: Adverse outcomes associated with the use of drotrecogin alfa (activated) in patients with severe sepsis and baseline bleeding precaution, Critical Care Medicine, 2009*), which reported an increased risk of serious bleeding events and of death in patients with sepsis and baseline bleeding risk

factors who received the product.

The current prescribing information for the drug describes the increased risk of bleeding. The Agency says that overall, the finding by the study is consistent with the information in the current product label. Prescribers have been advised to refer to the product label for the specific contraindications, warnings and precautions and carefully weigh the increased risk of bleeding against the benefits of the drug.

*(See WHO Pharmaceuticals Newsletters No. 2 and No. 3, 2005 for the use of drotrecogin alfa in Canada and USA, and in Europe.)*

***Reference:***
*Early Communication about an Ongoing Safety Review, US FDA, 4 February 2009* (www.fda.gov).

## Ezetimibe

### Emerging evidence of association with pancreatitis

**New Zealand.** According to Medsafe, there is emerging evidence that ezetimibe can cause pancreatitis. There are proportionately more reports of pancreatitis with ezetimibe than with statins, in the Centre for Adverse Reactions Monitoring database. It is known that anti-HIV agents, statins, tetracyclines and valproate are associated with acute pancreatitis. Prescribers have been advised that if acute pancreatitis is confirmed, the suspect medicine should be discontinued and supportive treatment initiated.

***Reference:***
*Prescriber Update Vol. 30, No.1 February 2009* (www.medsafe.govt.nz).

## Methylphenidate

### Updated guidance

**Europe.** The EMEA has concluded that methylphenidate-containing medicines remain suitable for the treatment of children aged six years or older and adolescents with attention deficit/hyperactivity disorder (ADHD).

The EMEA's Committee for Medicinal Products for Human Use (CHMP) has reviewed the benefits and risks of methylphenidate after recent concerns about cardiovascular risks, cerebrovascular risks, psychiatric safety and its long-term effects. Following the reviews, the CHMP concluded that there was no need for an urgent restriction on the use of methylphenidate-containing medicines, but that new recommendations on prescribing the medicines and on pre-treatment screening and ongoing monitoring of patients are needed to maximize the safe use of these medicines. All patients should be screened for any problems with blood pressure or heart rate and psychiatric disorders before starting treatment and monitored regularly during treatment. Treatment should be interrupted at least once a year to determine whether continuation is needed. In addition, the CHMP asked that further studies be carried out, particularly into the long-term effects of methylphenidate.

*(See WHO Pharmaceuticals Newsletter No. 4, 2006 for revision of labelling for ADHD drugs in Canada.)*

***Reference:***
*Press Release, EMEA, 22 January 2009* (www.emea.europa.eu).

## Non-steroidal anti-inflammatory drugs

### Cardiovascular risk

**UK**. MHRA has informed health-care professionals of the results of two recent epidemiological studies on the thrombotic cardiovascular risk associated with use of non-steroidal anti-inflammatory drugs (NSAIDs) in the general population. These new studies have found an increased cardiovascular risk with all users of NSAIDs, not only those with baseline risk factors and not only chronic users. However, the greatest concern relates to chronic use of high doses, especially for coxibs and diclofenac. The Agency says that the findings support current advice that patients should use the lowest effective dose and for the shortest duration necessary to control symptoms.

In addition, MHRA has explained that naproxen is associated with a lower thrombotic risk than coxibs, and for ibuprofen, no significant risk has been identified for doses up to 1200 mg daily.

***Reference:***
*Drug Safety Update, MHRA, Volume 2, Issue 7, February 2009* (www.mhra.gov.uk).

## Proton pump inhibitors

### Possible risk of fracture

**Australia.** According to the *Australian Adverse Drug Reactions Bulletin*, to date, three large retrospective studies have suggested an association

between proton pump inhibitors (PPIs) and an increased incidence of fractures, although further study is necessary to verify the association. In Australia, there have been only two reports of cases where a PPI has been associated with a pathological fracture and/or osteoporosis, and the PPI was the sole suspect in only one of these cases. PPIs (omeprazole, pantoprazole, lansoprazole, rabeprazole and esomeprazole) have been available in Australia since the mid 1990s.

ADRAC says that despite the limitations of the available data, it would be reasonable to consider the potential for increased fracture risk, and has advised clinicians to prescribe the lowest effective dose for recognized indications and periodically re-evaluate individual cases to determine whether PPI therapy remains necessary.

***Reference:***
*Australian Adverse Drug Reactions Bulletin, Volume 28, Number 1, February 2009* (www.tga.gov.au).

## Selective serotonin re-uptake inhibitors

### Increased risk of suicidality

**New Zealand.** Medsafe has issued advice to prescribers about the risks and benefits associated with selective serotonin re-uptake inhibitors (SSRIs) when used to teat major depressive disorder (MDD) in children and adolescents. The advice includes the finding that all SSRIs have consistently been associated with an increase in suicidality in meta-analyses of clinical trials of the use of SSRIs to treat MDD in children and adolescents. It was advised that antidepressant use should be considered in consultation with a psychiatrist or paediatrician, and that particular care should be taken in the period shortly after initiating antidepressant treatment, after a change in dosage, and after discontinuing treatment.

*(See WHO Pharmaceuticals Newsletters No.3, 2005 and No.6, 2004 about risk of suicidal behaviour in children and adolescents in Europe and Australia respectively.)*

***Reference:***
*Prescriber Update Vol. 30, No.1, February 2009* (www.medsafe.govt.nz).

## Tibolone

### Increased risk of breast cancer recurrence

**UK**. Tibolone increases the risk of breast cancer recurrence in women with a history of breast cancer, according to *Drug Safety Update*. Tibolone is a synthetic hormone therapy for first-line treatment of menopausal symptoms and for second-line prevention of osteoporosis in women at high risk. MHRA explains that the LIBERATE (randomized controlled trial), which was designed to investigate whether tibolone is effective and safe to use in women with a history of breast cancer, was stopped early because it identified a significantly increased frequency of breast cancer recurrence in the tibolone group compared with the placebo group.

Tibolone is contraindicated in women with known or suspected breast cancer and those with a history of breast cancer. Health-care professionals have been advised not to use tibolone (or conventional hormone-replacement therapy) in women with known or suspected breast cancer, or in those with a history of breast cancer.

***Reference:***
*Drug Safety Update, MHRA, Volume 2, Issue 7, February 2009 (www.mhra.gov.uk).*

## Topical anaesthetics

### Association with serious adverse events

**Canada.** Important safety information has been issued about the association of excessive application of topical anaesthetics with serious adverse events.

Health-care professionals have been informed the following.
• Serious adverse reactions including methaemoglobinaemia, central nervous system toxicity and cardiovascular collapse have been associated with application of topical anesthetics to large surface areas of the body, often in preparation for laser removal of body hair.
• Patients are more likely to experience serious side effects from a topical anesthetic if they use it on a large area of their body, if they apply it to abraded or diseased skin or if they occlude the treated area with plastic wrap or other dressing.
• Children should be closely observed during and after use of topical anesthetics, as they may be at greater risk than adults for serious adverse events.

Systemic toxicity from local anesthetics may include cyanosis, headache, drowsiness, respiratory depression, confusion, convulsions, bradycardia, hypotension and cardiac arrhythmias.

*(See WHO Pharmaceuticals Newsletter No. 1, 2009 for*

*information on a related public health advisory in USA.)*

***Reference:***
*Advisories, Warnings and Recalls, Health Canada, 13 January 2009*
(*www.hc-sc.gc.ca*).

## Unauthorized tanning product

### Safety alert against purchase via the internet

**Ireland.** The Irish Medicines Board (IMB) has issued a safety alert on Melanotan, which is an unauthorized medicine marketed through the internet as a drug that purports to assist tanning. The IMB warns that this product poses the risk of infection owing to microbial contamination found in the product as well as no evidence that it is safe or effective.

The IMB advises consumers to stop using the product immediately and consult their pharmacist or doctor. The Agency also advises consumers not to purchase any medicinal product on the internet.

***Reference:***
*Press Statement, IMB, 27 February 2009*
(*www.imb.ie*)

# Nineteenth Meeting of the Global Advisory Committee on Vaccine Safety, 17-18 December 2008

The Global Advisory Committee on Vaccine Safety (GACVS), established by WHO in 1999 to respond promptly, efficiently, and with scientific rigour to vaccine safety issues of potential global importance, met on 17–18 December 2008. Among topics discussed were the safety profiles of rotavirus and human papillomavirus vaccines.

**Rotavirus vaccines**

The Committee was presented with post-marketing information on the Rotateq and Rotarix vaccines from Australia, Latin America and the United States. Given the data presented, members were reassured that a risk of intussusception of the order of that which had been associated with Rotashield could be ruled out with confidence. The Committee also indicated, however, that the available post-marketing surveillance data were still too few to rule out, with confidence, a risk of substantially lower magnitude. The Committee emphasized the importance of continuing to accumulate post-marketing surveillance data on intussusception and other possible adverse effects and stressed the importance of setting up surveillance systems for such effects as the vaccines were introduced into increasing numbers of developing countries.

**Human papillomavirus (HPV) vaccines**

The Committee reviewed the latest recommendations of the WHO Strategic Advisory Group of Experts on immunization on HPV vaccines as well as data related to their large-scale use and articles on early post-marketing surveillance. After careful methodological review of the evidence, GACVS concluded that none of the reports raised sufficient concern to change previous advice given by GACVS.

Given that many countries have only recently introduced HPV vaccines at the national level, and as plans exist to introduce the vaccines in many countries with varying capabilities for monitoring of adverse events following immunization, the Committee called for increased attention to building capacity for post-marketing surveillance in those countries where introduction is planned. The Committee also agreed to comprehensively review the post-marketing safety profile of HPV vaccines during 2009.

Full report - *http://www.who.int/wer/2009/wer8405.pdf*